

CXLV. THE INFLUENCE OF PROLONGED MUSCULAR REST ON METABOLISM.

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WHEREAS an extensive literature has grown around the question of the influence of work on metabolism, there is one phase of metabolism which has received but little attention, namely, the metabolic changes produced by prolonged muscle rest. This was specially brought home to the present writer while investigating the changes occurring in the mineral metabolism during the healing of fractured bones. It was noted that while there was usually a slight negative balance of calcium, there was an excessive loss of phosphorus, which, during the second week of healing, for example, amounted in some cases to an average of 2.6 g. P_2O_5 daily. Was this excessive loss of phosphorus the result of a local mineral change at the site of fracture, involving a retention of calcium and loss of phosphorus, or was it, on the other hand, the result of the wasting or spasm of muscle, either alone, or accompanied by an atrophy of bone? Determinations of the nitrogen balance further revealed that there was an excessive loss of this element, and it was obvious that before one could attempt to interpret these changes in patients suffering from fractures, it was necessary to gain some insight into the more fundamental problem of the disturbed metabolism produced by prolonged rest.

Although the maintenance of normal functional activity necessitates a balance between anabolism and catabolism it is, however, almost impossible to define what this normal balance is. Different individuals who resemble each other in muscular build may have very different levels of functional activity, which they term their normal routine. The experiments which are to be described were designed to produce such a lowering of muscular metabolism as to be definitely below any arbitrary "normal." They are concerned with pure disuse atrophy, and not with atrophy due to destructive lesions of the lower motor neurons or their axons, or to toxic action, or to pressure. It has long been observed that muscular wasting associated with bone or joint disease is more rapid and extreme than that which occurs with simple disuse of a limb. In the former, visible loss of substance may be seen in a day or two. It is quite definite also, that there is a more rapid and extreme wasting in limbs immobilised for some inflammatory or traumatic lesion,

than in limbs immobilised to correct a deformity. Harding [1925, 1926, 1929] has thrown some light on this problem. She found that the oxygen consumption of muscles wasted as the result of arthritis is definitely increased above normal; whereas that of muscles wasted from pure disuse is unaltered. Further, that to produce the first type of atrophy experimentally, there must be complete integrity of the afferent nervous paths, and that the atrophy of pure disuse can be still produced even after de-afferentation at the posterior columns. There appear then to be two quite distinct types of atrophy—one which is mainly of reflex origin, and one which is probably entirely due to imposed rest.

Observations such as those of Ollerenshaw [1925] and Smith [1928] throw considerable doubt on the adequacy of our conceptions of the mechanism of disuse. These authors describe three cases of congenital absence of the tibia, where the *tibiofibularis* muscle had only one attachment. During life they subserved no function, and were unable to shorten; nevertheless they persisted without atrophy or degeneration. The oldest subject was 13 years old at the time of amputation. On the other hand, Lipschütz and Audova [1921] state that section of the *tendo Achillis* in rabbits causes an atrophy of muscle which is nearly as great as that caused by nerve sections. They believe that atrophy is due to a great decrease of work performed. Incisions of muscle and tendon without complete section did not produce such pronounced effects.

On reviewing the literature on the chemical side, it is surprising to find how little this aspect of metabolism has been studied. As early as 1855 [Beigel, 1855] had compared the urinary excretions of four healthy subjects during periods of active recreation and of comparative rest. The average daily output of urea during the period of active movement was 52.26 g., and during the period of rest on a sofa 46.10 g. Shaffer [1908] made observations on a man who spent 2 days wholly in bed, and then on the following 4 days got up for a few hours to sit in a chair. The rest was sufficient to weaken the patient noticeably. This period was followed by one of normal activity. The average total daily nitrogen excretion was 4.77 g. and 4.40 g., while the sulphur excretion was 0.438 g. and 0.424 g. respectively, during these two periods. There does not appear to have been any pre-rest period to ensure that nitrogen equilibrium was established. Shaffer, however, concludes "that either increase or decrease of muscular activity within physiological limits has *per se* no effect on protein metabolism as indicated by the urinary excretion of nitrogen and sulphur."

That the problem is complicated by an atrophy of bone has been shown by Allison and Brooks [1921, 1922], who found that the amount of bony change varied with the degree of disuse, the cause of the disuse being immaterial.

General plan of the experiments.

The subjects of the present series of experiments were either volunteers in perfect health, or were patients admitted to hospital with loose fragments of cartilage in the knee-joint. These latter, apart from occasional locking of the knee-joints, suffered no discomfort, and were in good health. They were allowed to select the quality and quantity of foodstuffs they desired from a prepared list. This intake, as well as the intake of water, was kept constant during the course of the experiment, except where expressly stated. The urine was collected in 24-hourly specimens, made up to a constant volume, and preserved with thymol in chloroform. The various periods during which faeces were collected were marked off with carmine, taken in the form of capsules. The faeces were dried on a steam-bath and in an air-oven before being stored in sealed bottles. A pre-period of 4 to 5 days was usually allowed in order to obtain nitrogenous equilibrium. During this pre-rest period, the subjects led a sedentary life, performing the ordinary routine of the ward. In Exp. 1, however, the level of activity, though higher, was still very constant. When nitrogenous equilibrium was obtained, the subject was confined to bed, with one lower limb encased in a well-padded osteotomy splint, the foot-piece being anchored. In some of the experiments, the activity of the other leg was limited by being loosely attached to a sand-bag. No massage was allowed, and only occasionally were the splints readjusted. The subjects were propped up in bed, and asked to limit, as far as possible, all superfluous movements.

*Analytical methods.**(a) Urine:*

Total acidity:	Expressed as cc. 0.1 <i>N</i> acid in 24 hrs.
Total nitrogen:	Kjeldahl method.
Urea:	Urease method.
Ammonia and creatinine:	Folin's method.
Uric acid:	Benedict and Franke's method [1922].
Total sulphur:	Denis's modification of Benedict's method.
Inorganic sulphur and ethereal sulphur:	Folin's method.
Neutral sulphur:	By difference.
Total phosphorus:	Neumann's wet ash method.
Calcium and magnesium:	Shohl and Pedley's method [1922].

(b) Faeces and food:

Total nitrogen:	Kjeldahl method.
Total sulphur:	Material extracted and evaporated to dryness with HNO_3 and then with HCl , then Denis's modification of Benedict's method applied.

Phosphorus:	Material ashed in the presence of excess $\text{Ca}(\text{OH})_2$: phosphorus precipitated as ammonium phosphomolybdate and weighed directly.
Calcium:	Material ashed, any iron removed, then precipitated according to Shohl and Pedley's method.
Magnesium:	Shohl and Pedley's method.

Exp. 1. The subject, G.P., a university student in perfect condition, offered his services for experimentation. During the first 5 days, he maintained the same level of activity, 1 hour a day being spent walking rapidly in the open. On the fifth day of diet he was confined to bed, with his left leg in a long osteotomy splint, the foot piece being anchored. The right leg was held down by being loosely attached to a sand-bag. The subject lay thus in bed for 11 days.

In addition to the ordinary routine of the ward, on the first day of resumed activity he walked as briskly as possible for $1\frac{1}{2}$ hours; on the second for $2\frac{1}{2}$ hours; for $2\frac{3}{4}$ hours on the third; $1\frac{1}{2}$ hours on the fourth; and on the last day, approximately 16 miles were accomplished in the first 6 hours of the 24.

During the experimental period the patient's diet was constant. But on the second day of resumed activity, his fluid intake was increased by 200 cc. water, and on the fourth and fifth day, by 400 cc. each day.

Age 19 years; height 181 cm.; weight prior to imposed rest 71.52 kg.; weight immediately after imposed rest 68.66 kg.; weight after 4 days' resumed activity 68.20 kg.

Daily intake of food:

Dried milk:	55 g. (made up in fluid form from Cow and Gate half cream dried milk to 630 cc.).
Brown bread:	215 g.
Digestive biscuits:	90 g.
Fresh butter:	70 g.
Steak:	150 g. (served as stew).
Dried apples:	15 g. (served stewed).
Dried tomato soup:	15 g. (served as soup).
Dried egg:	9 g. (served as custard).
Tea:	400 cc.
Sugar:	25 g.
Marmalade:	1 level teaspoonful.
Juice of 1 orange:	

(Owing to an unavoidable delay in this experiment, a deposition of phosphates had occurred in the urines, before the phosphorus could be estimated. The urinary phosphate figures are therefore omitted.)

Exp. 2. The subject, J.M., a coal-miner, was in good health, and apart from a loose piece of cartilage in one knee, was physically sound. He walked

Table I. (*Exp. 1.*)

State	Vol. of urine cc.	Nitrogen g.				Faeces (daily av.)	Sulphur (SO ₃) g.				P ₂ O ₅ g. Faeces (daily av.)	Calcium CaO g.	
		Total	Uric acid	Crea- tinine			Total	Inor- ganic	Ethe- real	Neutral		Urine (daily av.)	Faeces (daily av.)
A	1190	12.32	—	—	1.148 19.79	—	—	—	—	0.897	0.326	0.694	
A	1160	13.44	—	—		—	—	—	—				
A	1040	12.54	0.347	0.651		2.09	—	—	—				
A	1080	12.51	0.335	0.654		2.08	—	—	—				
A	1200	12.40	0.369	0.588	1.160 19.18	2.08	1.537	0.175	0.372	0.894	0.388	0.809	
1 R	1455	11.31	0.377	0.678		1.82	—	—	—				
2 R	1620	11.46	0.410	0.674		2.04	—	—	—				
3 R	1140	11.40	0.346	0.688		2.03	—	—	—				
4 R	1220	12.77	0.362	0.678	1.185 19.51	2.22	—	—	—	0.960	0.438	0.957	
5 R	1210	14.00	0.382	0.481		2.33	—	—	—				
6 R	1200	14.22	0.389	0.617		2.26	—	—	—				
7 R	1560	15.45	0.413	0.678		2.48	—	—	—				
8 R	1400	13.66	0.394	0.708	1.185 19.51	2.32	—	—	—	0.960	0.365	0.957	
9 R	1590	14.78	0.406	0.698		2.46	—	—	—				
10 R	1670	14.24	0.407	0.700		2.38	—	—	—				
11 R	1580	14.78	0.369	0.625		2.52	2.000	0.135	0.390				
1 A	1400	12.21	0.353	0.678	1.185 19.51	2.45	—	—	—	0.960	0.365	0.957	
2 A	1280	15.01	0.373	0.688		2.56	—	—	—				
3 A	1340	12.87	0.335	0.676		2.25	—	—	—				
4 A	1300	13.77	0.368	0.674		2.50	—	—	—				
5 A	1320	13.60	0.362	0.678	2.51	—	—	—	—	—	—	—	
Intake		13.51				2.22				1.212			

Average daily excretion of faecal solids in heavy type under value for average daily excretion of faecal nitrogen for same period.

A = active state. R = resting state.

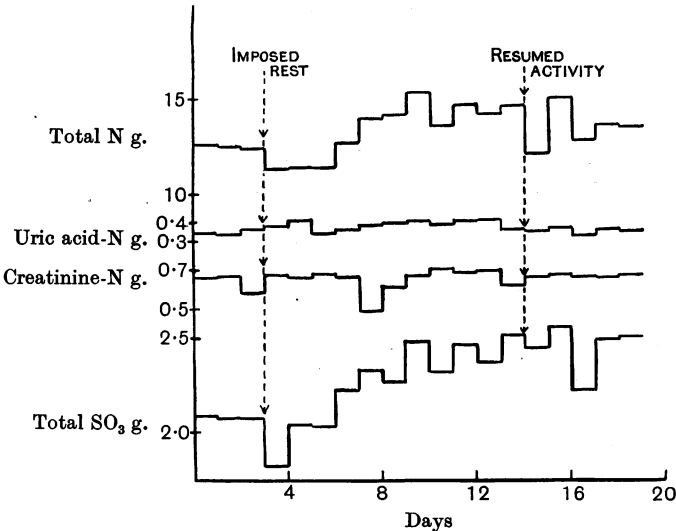


Fig. 1. Experiment 1.

about the ward till the fifth day, when he was confined to bed with an osteotomy splint, extending to a few inches above the knee. From the ninth day of rest onwards, an orange was added to the diet. On the tenth day, castor oil was given in preparation for the operation, which, however, was not performed till the thirteenth day. Stovaine spinal anaesthesia was used. From

the day of the operation till the twelfth day thereafter, the patient lay quietly in bed, his left leg kept at rest between two sand pillows. The operation clips were removed on the tenth day. On the thirteenth day after operation the patient was allowed up for 1 hour, and on the days following for longer intervals. On the third day of resumed activity, it was noticed that a small haematoma had formed in the wound, the bandages being stained with blood.

Age 28 years; height 182 cm.; weight 66.7 kg. at start.

Daily intake of food:

Dried milk:	105 g.	Dried lentil soup:	15 g.
Brown bread:	200 g.	Dried egg:	9 g.
Digestive biscuits:	90 g.	Tea:	400 cc.
Fresh butter:	70 g.	Sugar:	25 g.
Steak:	100 g.	Juice of 1 orange.	
Dried apples:	15 g.	Marmalade:	1 level teaspoonful.

Table II. (*Exp. 2.*)

State	Vol. of urine cc.	Nitrogen g.				Faeces (daily av.)	Sulphur (SO ₃) g.				P ₂ O ₅ g.	Calcium CaO g.		
		Total	Urea	Am- monia	Crea- tine		Total	Inor- ganic	Ethe- real	Neutral	Urine	Faeces (daily av.)	Urine (daily av.)	Faeces (daily av.)
A	1050	11.87	—	0.480	0.561	1.276	2.05	—	—	—	2.17	1.18	0.374	1.649
A	1100	11.93	9.72	0.431	0.541		1.94	1.41	0.19	0.34	2.57			
1 R	1420	10.41	8.25	0.440	0.488		1.83	—	—	—	1.99			
2 R	1005	11.81	9.42	0.482	0.611		2.19	—	—	—	2.37			
3 R	1020	15.00	—	—	0.669		2.47	—	—	—	2.93			
4 R	950	13.32	—	—	0.558		2.27	—	—	—	2.81			
5 R	1450	12.76	—	—	0.502		2.08	—	—	—	2.65			
6 R	1000	12.20	—	—	0.511		2.10	—	—	—	2.98			
7 R	1500	14.44	—	—	0.539		2.33	—	—	—	3.49			
8 R	1380	13.75	—	—	0.578		2.41	—	—	—	2.83			
9 R	966	14.00	—	—	0.542	2.39	—	—	—	3.09				
Castor oil														
A	840	12.54	—	—	0.561	2.23	—	—	—	3.41				
A	1080	14.00	—	—	0.589	2.45	—	—	—	2.49				
1 R	1200	12.88	—	—	0.545	2.28	—	—	—	2.47				
2 R	1450	13.88	—	—	0.601	2.51	—	—	—	2.57				
3 R	1000	13.87	—	—	0.609	2.31	—	—	—	2.77				
4 R	1220	13.66	—	—	0.600	2.47	—	—	—	2.01				
5 R	1175	15.23	—	—	0.641	2.94	—	—	—	2.95				
6 R	1040	12.43	—	—	0.365	2.18	—	—	—	2.45				
7 R	1580	14.56	—	—	0.700	3.26	—	—	—	3.79				
8 R	1660	17.92	—	—	0.657	2.94	—	—	—	3.95				
9 R	1760	18.27	—	—	0.610	2.99	—	—	—	3.32				
10 R	1830	19.32	—	—	0.548	3.32	—	—	—	3.33				
11 R	1890	19.60	—	—	0.532	3.41	—	—	—	3.65				
12 R	1930	20.14	—	—	0.600	3.65	—	—	—	3.89				
1 A	1970	20.14	1648	0.709	0.638	3.66	—	—	—	3.83				
2 A	1630	21.42	1820	0.841	0.630	3.81	2.96	0.13	0.72	3.51				
3 A	1735	22.54	1840	1.031	0.709	3.91	3.21	0.15	0.70	3.90				
4 A	1560	17.36	1525	1.052	0.591	2.97	—	—	—	2.91				
Intake		13.29				2.20				3.76	1.917			

Exp. 3. This man, J.C., a "jack of all trades," who, 2½ months previously, had had a loose body removed from his knee, and had completely recovered, offered himself as a subject. The experimental period had to be abandoned on the sixth day of imposed rest. The diet was similar in quality and quantity to that described in *Exp. 2.*

Age 40 years; height 167 cm.; weight 68.2 kg. at start.

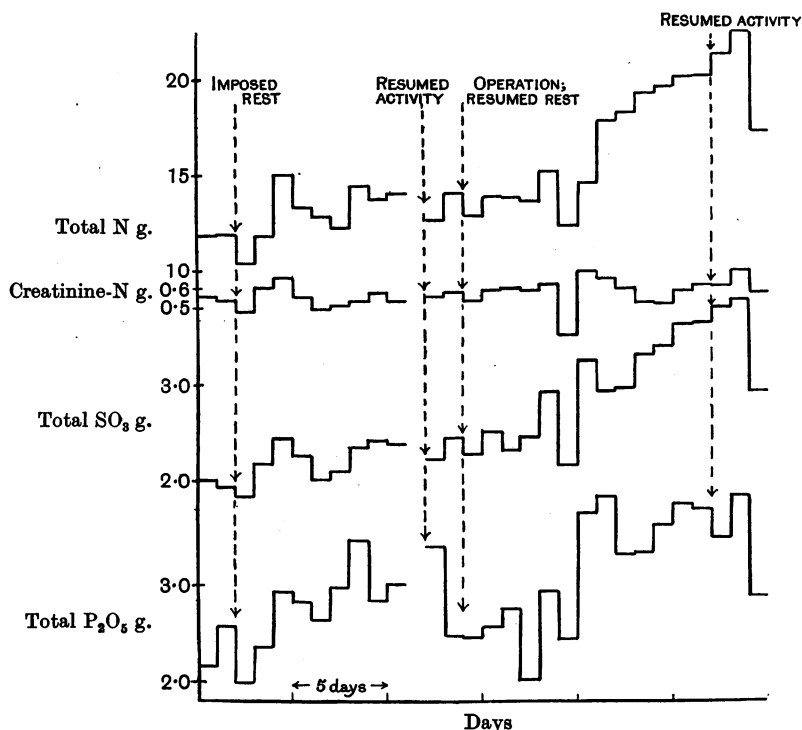


Fig. 2. Experiment 2.

Table III. (*Exp. 3.*)

State	Volume of urine cc.	Nitrogen g.		Sulphur SO ₂ g.			
		Total	Creatinine	Total	Inorganic	Ethereal	Neutral
A	—	9.57	—	—	—	—	—
A	1045	12.97	0.44	2.18	—	—	—
A	980	11.34	0.44	1.93	1.56	0.17	0.20
1 R	1310	10.77	0.44	1.79	—	—	—
2 R	—	8.94	0.41	1.50	—	—	—
3 R	1420	11.73	0.57	1.99	—	—	—
4 R	1360	12.35	0.41	2.06	—	—	—
5 R	1400	12.72	0.44	2.10	1.67	0.24	0.19
6 R	1410	13.86	0.53	2.36	1.70	0.25	0.41
Intake		13.29		2.20			

Exp. 4. The subject, J.C., was the same as in *Exp. 3*, and the procedure was similar to that adopted in that experiment. With the exception of dried lentil soup, which was substituted for tomato soup, the diet was identical. The time interval between *Exps. 3* and *4* was 1 month.

Exp. 5. This female subject, E.M., a cook, had been confined to bed at home for a week prior to admission, with a partially loose fragment of semi-lunar cartilage in her knee-joint. The knee was slightly swollen, otherwise she was in good health. For the first 4 days of residence in hospital she walked a little about the ward, after which she was confined to bed, with a splint encasing her leg. The patient commenced to menstruate on the fourth day after the completion of the experimental period.

Table IV. (*Exp. 4.*)

State	Titratable acidity N/10 cc.	Nitrogen g.					Sulphur (SO ₃) g.				P ₂ O ₅ g.		Calcium CaO g.	
		Total	Urea	Am- monia	Crea- tinine	Faeces (daily av.)	Total	Inor- ganic	Ethe- real	Neutral	Urine	Faeces (daily av.)	Urine (daily av.)	Faeces (daily av.)
A	—	12.09	—	—	—	—	—	—	—	—	—	—	—	—
A	356	12.09	10.11	0.421	0.562	1.169	1.99	1.56	0.162	0.270	2.08	1.302	0.385	1.537
A	352	12.09	10.08	0.402	0.567		2.10	1.61	0.224	0.259	2.43			
1 R	320	10.33	8.50	0.331	0.611		2.01	1.54	0.123	0.345	2.18			
2 R	452	13.52	11.68	0.429	0.640		2.45	1.86	0.119	0.373	2.48			
3 R	370	12.45	10.52	0.360	0.509		2.13	1.67	0.122	0.366	2.39			
4 R	403	12.60	10.80	0.391	0.561		2.22	1.81	0.262	0.145	2.74			
5 R	370	13.35	11.40	0.402	0.570		2.32	1.81	0.137	0.371	2.54			
6 R	417	13.10	11.40	0.409	0.582		2.07	1.67	0.133	0.273	2.54			
7 R	409	12.60	10.80	0.455	0.628		2.15	1.73	0.162	0.259	2.82			
8 R	409	13.86	11.80	0.471	0.621		2.38	1.94	0.147	0.299	2.70			
9 R	328	13.23	11.15	0.440	0.509		2.32	1.82	0.112	0.385	2.41			
10 R	385	13.48	11.70	0.441	0.555		2.28	1.89	0.158	0.234	2.66			
11 R	367	13.35	11.05	0.440	0.573	2.24	1.81	0.262	0.170	2.53				
12 R	428	13.23	11.28	0.462	0.572	2.29	1.90	0.137	0.259	2.52				
Intake		13.28						2.20				3.79	1.957	

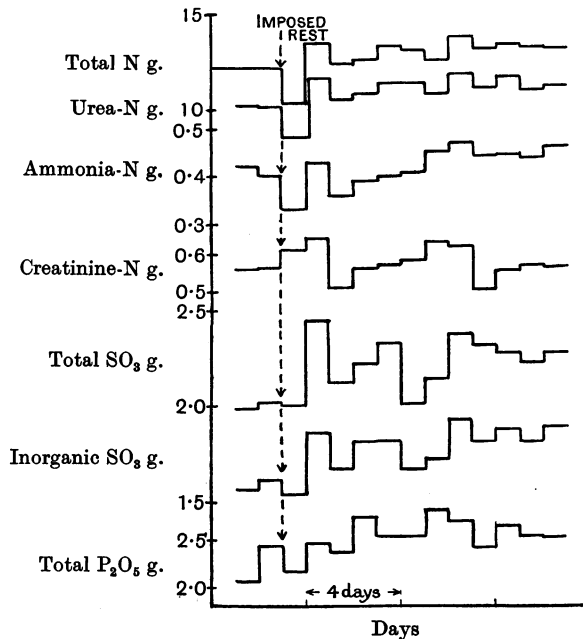


Fig. 3. Experiment 4.

Age 19 years; height 162 cm.; weight 50 kg. at start.

Daily intake of food:

Dried milk:	55 g.	Dried egg:	9 g.
Brown bread:	135 g.	Tea:	200 cc.
Digestive biscuits:	90 g.	Sugar:	15 g.
Fresh butter:	70 g.	Juice of 1 orange.	
Dried tomato soup:	50 g.	Marmalade:	1 level dessertspoonful.

Table V. (*Exp. 5.*)

State	Total nitrogen	Total sulphur (SO ₃)	Total phosphorus P ₂ O ₅
A	8.32	—	—
A	6.30	1.12	1.73
A	6.40	1.21	1.64
1 R	6.93	1.23	1.73
2 R	6.74	1.21	1.88
3 R	7.43	1.31	2.29
4 R	7.05	1.31	1.92
5 R	8.94	1.60	2.35
6 R	7.94	1.41	1.92
7 R	9.20	1.52	1.74
8 R	7.90	1.36	1.47

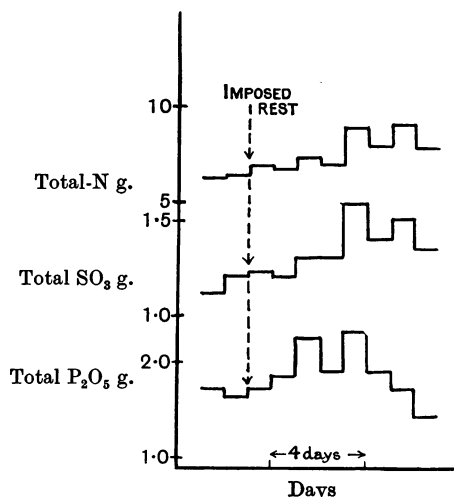


Fig. 4. Experiment 5.

Exp. 6. Subject, J.H., a miner in good physical condition, apart from occasional locking of one knee-joint, led a sedentary ward life for 3 days, prior to being confined to bed. No splint was used, and though the patient was not allowed up, he performed knee-bending exercises twice or thrice a day. Unfortunately, circumstances did not permit of a longer period of observation to decide what changes, if any, might ensue from confinement to bed without immobilisation. Following this experimental period, he was operated upon, being confined to bed for 10 days longer.

Age 20 years; height 165 cm.; weight 61.82 kg. at start.

Daily intake of food:

Dried milk:	55 g.	Dried apples:	15 g.
Brown bread:	200 g.	Tea:	400 cc.
Digestive biscuits:	90 g.	Sugar:	25 g.
Fresh butter:	40 g.	Juice of 1 orange.	
Steak:	200 g.	Marmalade:	1 teaspoonful.
Dried tomato soup:	15 g.		

Table VI. (*Exp. 6.*)

State	Volume of urine cc.	Total nitrogen g.
A	1220	14.00
A	1320	15.26
1 R + E	1750	13.58
2 R + E	1360	13.58
3 R + E	1150	12.18
4 R + E	1230	14.42
5 R + E	1340	13.72
6 R + E	1400	15.12
7 R + E	1290	14.00

A = active. R = resting. E = limited leg exercises.

Exp. 7. This female patient, M.G., a hawker, fractured her left humerus on 29. vi. 29. She led a sedentary life up till 15. vii. 29, when she was confined to bed, and was not allowed up for 32 days. Her urine was collected daily from the fifth day of rest till the eleventh day of resumed activity. The patient's movements in bed were in no way restricted. A menstrual period intervened in the course of the experiment. The resumed activity took the nature of sedentary ward life plus walking in the hospital precincts.

Age 37 years; height 156 cm.; weight 41.36 kg. without splint.

Table VII. (*Exp. 7.*)

State	Total urinary nitrogen. Daily average g.
5 R-11 R	8.75
12 R-17 R	8.65
Menstrual period.	
24 R-30 R	7.99
31 R-37 R	8.06
1 A- 5 A	8.40
6 A-11 A	8.80
Intake	9.28

Daily intake of food:

Dried milk:	55 g.	Steak:	100 g.
Brown bread:	175 g.	Tea:	400 cc.
Digestive biscuits:	90 g.	Sugar:	25 g.
Fresh butter:	60 g.	Juice of 1 orange.	
Dried tomato soup:	15 g.	Marmalade:	1 dessertspoonful.
Dried apples:	15 g.		

Exp. 8. The subject, M.A., in otherwise good health, suffered from a fractured tibia. He was kept on constant diet from the fifth day after fracture till his fourth day of resumed activity, a period of 48 days. His oxygen consumption was determined daily during this period (see Table X).

Age 20 years; height 180 cm.; weight 65.02 kg. on dismissal.

Table VIII.

Partition of											
		Nitrogen					Sulphur SO ₂				
Exp.	State	Total	Urea	Am- monia	Uric acid	Crea- tinine	Total	Inor- ganic	Ethereal	Neutral	State
I G.P.	A	12.45	—	—	0.35 (2.8)	0.63 (5.0)	2.08	1.58 (73.7)	0.17 (8.4)	0.37 (17.9)	A
	9 R-11 R	14.60	—	—	0.39 (2.1)	0.67 (4.5)	—	—	—	—	
							2.52	2.00 (79.2)	0.13 (5.4)	0.39 (15.4)	11 R
	4 A- 5 A	13.68	—	—	0.36 (2.6)	0.67 (4.9)	—	—	—	—	
II J.M.	A	11.93	9.72 (81.5)	0.43 (3.6)	—	0.54 (4.5)	1.94	1.41 (72.7)	0.19 (9.8)	0.34 (17.5)	A
	25 R	20.14	16.48 (81.8)	0.71 (3.5)	—	0.64 (3.1)	—	—	—	—	
							3.81	2.96 (77.7)	0.13 (3.4)	0.72 (18.9)	1 A
	3 A	17.36	15.25 (87.8)	1.05 (6.0)	—	0.59 (3.4)	—	—	—	—	
IV J.C.	A	12.09	10.11 (83.4)	0.42 (3.4)	—	0.56 (4.7)	2.05	1.59 (77.6)	0.19 (9.2)	0.27 (13.2)	A
	10 R-12 R	13.35	11.34 (84.9)	0.45 (3.3)	—	0.56 (4.2)	2.26	1.86 (82.3)	0.20 (8.9)	0.20 (8.9)	11 R

Figures in brackets are percentages.

Table IX.

Urinary ratios; sulphur : nitrogen.

Experiment	State	Days	Total output	Excess output	Retention	Excess output
I G.P.	A	1- 3	1: 14.96	—	—	—
	R	1- 6	1: 14.80	1: 3.69	—	—
	R	7-11	1: 14.98	1: 15.16	—	—
	A	1- 5	1: 13.74	1: 6.87	—	—
II J.M.	A	1- 2	1: 14.87	—	—	—
	R	1- 5	1: 14.60	1: 11.31	—	1: 5.26
	R	6- 9	1: 14.73	1: 13.80	—	—
	A R	A- 7	1: 13.57	1: 8.50	—	—
	R A	8- 3 A	1: 14.39	1: 13.72	—	—
	A	4	—	1: 14.08	1: 13.78	—
III J.C.	A	1- 2	1: 14.69	—	—	—
	R	1- 6	1: 14.91	1: 26.48	—	—
IV J.C.	A	1- 2	1: 14.74	—	—	—
	R	1- 6	1: 14.27	1: 7.81	—	—
	R	7-12	1: 14.59	1: 13.25	—	—
V E.M.	A	2- 3	1: 13.59	—	—	—
	R	1- 8	1: 14.19	1: 17.68	—	1: 6.23

NITROGEN METABOLISM.

A practically constant excretion of urinary nitrogen was in existence in all cases prior to the super-imposition of the rest period. With the exception of Exp. 5, there was a drop in the excretion of urinary nitrogen on the first day of complete rest, and this was maintained sometimes for 1 or 2 days longer. The fact that there was no drop in this particular experiment may have been due to the patient's previous period of rest in bed. Following this initial diminution in nitrogen excretion, there is in all cases a distinct rise in

the urinary nitrogen, which is maintained irregularly. In Exp. 1, in the first days of imposed rest, there was a total excess output of 10·79 g. nitrogen in 11 days; in Exp. 2, 10·59 g. in 9 days; in Exp. 3, 2·33 g. in 6 days; in Exp. 4, 10·02 g. in 12 days; and in Exp. 5, 11·33 g. in 8 days.

Table X.

Gaseous metabolism.

Exp. 1. Subject: G.P. Oxygen consumption				Exp. 8. Subject: M.A. Oxygen consumption			
State	cc. D.B.	cc. Sp.	R.Q.	State	cc. Sp.		
A	288	—	0·761	5 R-11 R	234		
A	289	290	0·779		(+ 10 % , - 12 %)		
A	286	281	0·763				
1 R	283	295	0·772	12 R-18 R	219		
2 R	276	280	0·776		(+ 5·1 % , - 11 %)		
3 R	270	279	0·755				
4 R	261	—	0·758	19 R-25 R	236		
5 R	253	257	0·804		(+ 3·3 % , - 3·0 %)		
6 R	259	—	0·777				
7 R	242	242	0·818	26 R-32 R	235		
8 R	—	239	—		(+ 3·4 % , - 5·3 %)		
9 R	255	264	0·818				
10 R	245	260	0·838	33 R-39 R	242		
11 R	244	241	0·840		(+ 3·3 % , - 2·5 %)		
1 A	242	248	0·884				
2 A	249	250	0·845	40 R-49 R	240		
3 A	—	245	—		(+ 2·1 % , - 0·9 %)		
4 A	258	265	0·785				
5 A	268	272	0·762	1 A- 4 A	244		
					(+ 1·6 % , - 0·8 %)		

D.B.=Douglas bag method.

Sp.=spirometric method.

In Exp. 2, during the days following the operation, there was a very marked rise in the output of urinary nitrogen, which, by the twenty-fifth day, had increased by almost 100 %. During this post-operation period, the patient's leg was not completely immobilised. Throughout the period, apart from a post-operative rise of 0·5°, there was no rise in body temperature. As it was not till the sixth day after operation that the nitrogen curve began to climb more steeply, it is probable that the effects of stovaine spinal anaesthesia and operative interference would have passed off. The possibility of some reflex trophic effect on muscle, accounting for this enormous rise in the excretion of nitrogen, cannot be discounted. It will be noticed also, that in this, as in some of the other experiments, the effect of resuming activity was not immediately noticeable, but that there was a lag period. The volume of urine passed during this latter period also rose, though the intake was unaltered, but was not of an order sufficient to suggest that the rise of nitrogen excreted might be the result of a washing out of the tissues; rather it suggested that the increased volume of urine was dependent on the increased excretion of solutes.

It can therefore be stated that muscular rest of the order described causes a practically immediate but small rise in the output of urinary nitrogen. As

the period of rest lengthens, it appears probable that the rate of increase is accelerated, but that eventually it declines to a more steady level, depending on the degree of immobilisation.

Distribution of nitrogen. The curve of the excretion of urea rises proportionately with that of total nitrogen. The excretion of ammonia, following the initial fall at the commencement of the rest period, takes longer to rise, but continues parallel to that of total nitrogen. It will be noticed that the total acidity also tends to rise (Exp. 4).

Spriggs [1907] found in primary muscular dystrophy that the diminution of creatinine in the urine was proportional to the muscular wasting. In the present series of experiments, the creatinine excretion was but little altered, a very slight rise sometimes being noted as the period of rest lengthened. Uric acid behaved similarly.

The excretion of faecal nitrogen and of total faecal solids remains practically constant (Exp. 1).

METABOLISM OF SULPHUR.

As early as 1881, Feder [1881] had noted that the sulphur of ingested protein was excreted earlier than the nitrogen. Rubner [1902], Hämäläinen and Helme [1907], and von Wendt [1907] in addition found that phosphorus followed the excretion of nitrogen. Wolf and Osterberg [1911] found a lag in the excretion of the sulphur of super-imposed egg-white, and Lewis [1916] found, on feeding starved dogs with meat, a lag in the sulphur output. Sherman and Hawk [1901], on the other hand, have shown an almost parallel excretion of sulphur and nitrogen. Cathcart and Burnett [1926] found that with moderately severe work the sulphur rose *pari passu* with the output of nitrogen. The accumulated evidence seems to indicate that it is the nutritive state of the organism at the time which determines the fate of the components of the ingested protein, but that normally there is a delay in the excretion of nitrogen [Wilson, 1925].

Just as the evidence based on the excretion of nitrogen indicates in these experiments an increased catabolism, so we find that the curves of the elimination of sulphur run closely parallel to that of total nitrogen, the sulphur, however, being excreted more rapidly than the nitrogen, as judged from the S : N ratios.

The rise in the output of sulphur is due to a slightly greater proportionate excretion of inorganic sulphates. There is a slight fall in the excretion of ethereal sulphates, the neutral sulphates remaining more constant.

Sulphur : Nitrogen ratios. The pre-rest values of all cases lay between 1 : 14.68 and 1 : 14.96, with the exception of Exp. 5, where the figure was 1 : 13.6. These ratios corresponded to the proportion of ingested sulphur and nitrogen which, in the majority of the experiments, was 1 : 14.9. In Exp. 5 the food intake was meat-free. With the exception of Exp. 3, the ratios of the total excess sulphur to nitrogen show the source of this loss to be

some sulphur-rich material. The ratio is highest during the early days of imposed rest. During the first 6 days of inactivity in Exp. 1 the excess output was 1 : 3.69. From the seventh to the eleventh days, it had fallen to 1 : 15.16. The other experiments provide additional evidence of a sulphur-rich source. The ratio of the excess output on the fourth day of resumed activity in Exp. 2 was 1 : 14.08, the ratio of the material which had stopped being excreted on that particular day being 1 : 13.78.

A possible explanation for the divergence of the S : N ratio in Exp. 3 may rest in the fact that the organism had only a very low reserve of sulphur, due to a previous period of immobilisation.

The generally accepted S : N ratio of muscle is 1 : 14. It is seen that non-use of the order described leads to a loss of sulphur and nitrogen, the source of the material being some sulphur-rich complex store material, which is probably intimately connected with muscle.

METABOLISM OF PHOSPHORUS.

As was indicated earlier in this paper, it was the excessive loss of phosphorus in fracture cases which drew the attention of the present writer to the question of the disturbed metabolism of inactivity. The rôle of phosphorus in metabolism has always presented great difficulties, and particularly the assessment of the relative sources of the excreted phosphorus. Benedict [1907] noted that in the case of starvation there was a tendency towards a much larger excretion of phosphorus in relation to nitrogen than occurs in the ordinary composition of flesh. The source of this extra phosphorus is generally believed to be bone.

The tables show that equilibration of phosphorus is much more difficult to attain than that of either nitrogen or sulphur. It was only on the day prior to the initiation of the rest periods in Exps. 2 and 4 that there was a definite correspondence between intake and output. In the previous note on the metabolism of sulphur, the known tendency of phosphorus to lag behind the excretion of both sulphur and nitrogen was discussed. Another factor which may have interfered in part with early equilibrium was the relative richness of the diets in phosphorus and calcium.

The curves of the urinary excretion of phosphorus run, with varying regularity, parallel to those of nitrogen. The excretion of faecal phosphorus (Exp. 1) is little altered. As the period lengthens, there is a slight rise, corresponding to the rise in calcium excretion.

The usually accepted ratio of P_2O_5 : N in muscle is 1 : 6.6. Assuming the intake of P_2O_5 as the basal figure, then the excess output of P_2O_5 during the first 7 days of rest in Exp. 2 is 1.16 g. The excess output of nitrogen during the same period is 6.64 g., using the urinary basal figure of 11.9 g. daily. The P_2O_5 : N ratio is 1 : 5.7. In Exp. 4, using similar methods, the ratio is very low, 1 : 14.3. In Exp. 5, the ratio of the urinary excess outputs is 1 : 6.23.

The data provided by these experiments are too inconclusive to allow us

to form a definite conception of the rôle of phosphorus in the metabolism of imposed rest. Longer periods of immobilisation are required before a clear result can be obtained.

METABOLISM OF CALCIUM.

Calcium equilibrium takes longer to attain than phosphorus. It was not attained in either Exps. 1, 2 and 4 until the period of inactivity was well advanced. There appeared to be a retention up to that point. Whether this was due to the high calcium content of the diet, or not, cannot be definitely stated. There appears to be a tendency for a loss of calcium to occur as the period of rest lengthens. The experimental data here do not warrant any more definite statement.

The experiments of Allison and Brooks [1921, 1922] have demonstrated by non-chemical methods that bone atrophy through disuse can readily take place.

It would appear essential that all experiments dealing with the metabolism of phosphorus and calcium must be of much longer duration and have much longer pre-periods than those dealing with the metabolism of nitrogen and sulphur.

GASEOUS METABOLISM.

The work of Hanriot and Richet [1888], Lehmann and Zuntz [1893], Benedict [1907], Takahira [1925] and Wishart [1927] has shown that during fasting the metabolism is very constant from day to day, even when the respiratory quotient is falling, but that essentially there is a reduction of metabolism. The data obtained in the course of the present series of experiments point to a similar constancy during prolonged muscular rest in the adequately fed subject. The diet of both subjects was kept constant from day to day, and all gaseous determinations were performed in the morning, with the subjects in the post-absorptive state, having lain quietly in bed for at least 12 hours. The subjects were well practised previously. In Exp. 1 determinations of the oxygen consumption were obtained both by the collection of expired air in a Douglas bag, with subsequent analysis in a Haldane's gas analyser, and with a calibrated spirometer of the Benedict-Collins type. The slightly greater facility of respiration in an open circuit compared with a closed one would account for the fact that the spirometric record is usually a little higher than that of the Douglas bag method. The maxima and minima percentage variations from the mean in the various periods of observations of subject M.A. during an experimental period of 48 days (Exp. 8) decreased progressively as the period lengthened, until they became practically negligible. From $\pm 11\%$ they dropped to $\pm 1.2\%$. Observations on a patient whose oxygen consumption was determined over a period of 40 days revealed, again, a gradual diminution from $\pm 14\%$ to $\pm 1.5\%$ in the maxima and minima percentage deviations from the mean of 6-day periods (data regarding

this patient are held over for a subsequent communication on the effect of massage on metabolism).

Since the level of activity is constant from day to day this gradual reduction in oscillation must be due to increased custom diminishing mental and physical disturbance. This point raises the question as to whether the latitude of $\pm 15\%$ day to day variation generally allowed in normals is due to insufficient practice.

Although in the subject G.P. there tended to be a slight but steady diminution in the oxygen consumption, which was accompanied by a rise in the respiratory quotient as the period of rest lengthened, this diminution did not fall below 17 % from the pre-rest values during the period of observation. A tendency for a fall in the oxygen consumption of subject M.A. was also noted, but thereafter the metabolism maintained a very constant level. In this connection, the work of Harding [1926] is interesting. She noted that the oxygen consumption of muscles wasted as the result of arthritis is definitely increased above normal, whereas that of muscles wasted from disuse is unaltered.

DISCUSSION.

In the present series of experiments, it has been demonstrated that prolonged rest in healthy subjects leads to a loss of nitrogen, sulphur, phosphorus, and in less degree, calcium. These changes must be reckoned as due to non-use of the body generally, and most probably to non-use of muscle and bone in particular.

Cathcart and Burnett [1926] and others have shown that moderately severe work produced a definite, though small, rise in the output of nitrogen and sulphur, signifying that the increased catabolism was in excess of any definite stimulation of anabolism. It is very curious that when the experimental conditions are changed to the other extreme, the urinary picture remains strikingly similar. That such a loss does not continue indefinitely during moderately severe periods of muscular work has been shown by Wilson. He has communicated to the present writer the results of a personal experiment, where a much longer period of work was performed, resulting in a fall of the curves to, and even below, the basal line. Surveying the results obtained in work-experiments with those of the present series on rest, it would appear that when one alters the level of functional activity there is a lag period before nitrogen equilibrium is again obtained. During this period there is a loss of the essentially active substance, which persists until, in the case of increased muscle work, the anabolic response is equal and opposite to, or even greater than, the increased catabolism. In the case of decreased muscular activity, it persists until the amount of functioning metabolic substance is reduced to such a level that the catabolism is equal and opposite to the diminished anabolism. Such a change does not appear to alter appreciably the endogenous metabolism as represented by uric acid and creatinine.

The reason for the absence of any immediate diminution of the urinary nitrogen and sulphur excretions on the resumption of activity in these experiments is probably that the anabolic response is masked by a sweeping-out of the catabolic products from the relatively stagnant tissues.

It appears reasonable to assume that the term "autolysis" may be applied to these processes in muscle. According to Morse [1914] disused muscle appears not to have any increased capacity for autolysis. Bradley [1918, 1922], however, has shown that voluntary muscle autolyses slowly and incompletely, and is influenced by the tissue reaction. He considers that, as a result of inadequate blood supply, the catabolic products accumulate, resulting in a rise in the H^+ ions within the cell, and a change from basic to acidic proteins. This activates the proteolytic enzymes, particularly the primary protease. The ereptase, previously inoperative, has now a suitable substrate, and the muscle mass decreases until equilibrium between the cell and its blood and lymph supply is re-established.

Such a hypothesis appears to offer a convenient description of the phenomena observed, but is it certain that the diminished blood supply is the cause and not yet another effect of the decreased metabolism? Any ultimate conception must interpret all these effects as being due to a primary biological necessity.

SUMMARY.

1. Subjects in nitrogenous equilibrium show, within a day or two from the commencement of a period of muscle rest of the order described, a rise in the excretion of sulphur, nitrogen, phosphorus, and calcium, in that order of priority. This loss is maintained fairly steadily for a varying period, after which it gradually declines.

2. The rise in the excretion of sulphur is due to a practically proportionate increase in inorganic sulphate. Ethereal sulphate tends to decrease, while neutral sulphur remains more constant.

3. The rise in the excretion of nitrogen is mainly due to a proportionate increase in the amount of urea. Ammonia excretion also rises, but more slowly. Creatinine and uric acid are practically unaltered.

4. The S : N ratio suggests a sulphur-rich source of the excreted material, presumably for the most part muscle.

5. Apart from a slight fall in the oxygen consumption, associated with a rise in the respiratory quotient, the gaseous metabolism remains very constant from day to day.

6. Maxima and minima percentage day to day variations in the oxygen consumption gradually decrease as the experimental period lengthens, from $\pm 14\%$ to $\pm 1.2\%$.

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